Plasma-Derived Products and Their Recombinant Analogues

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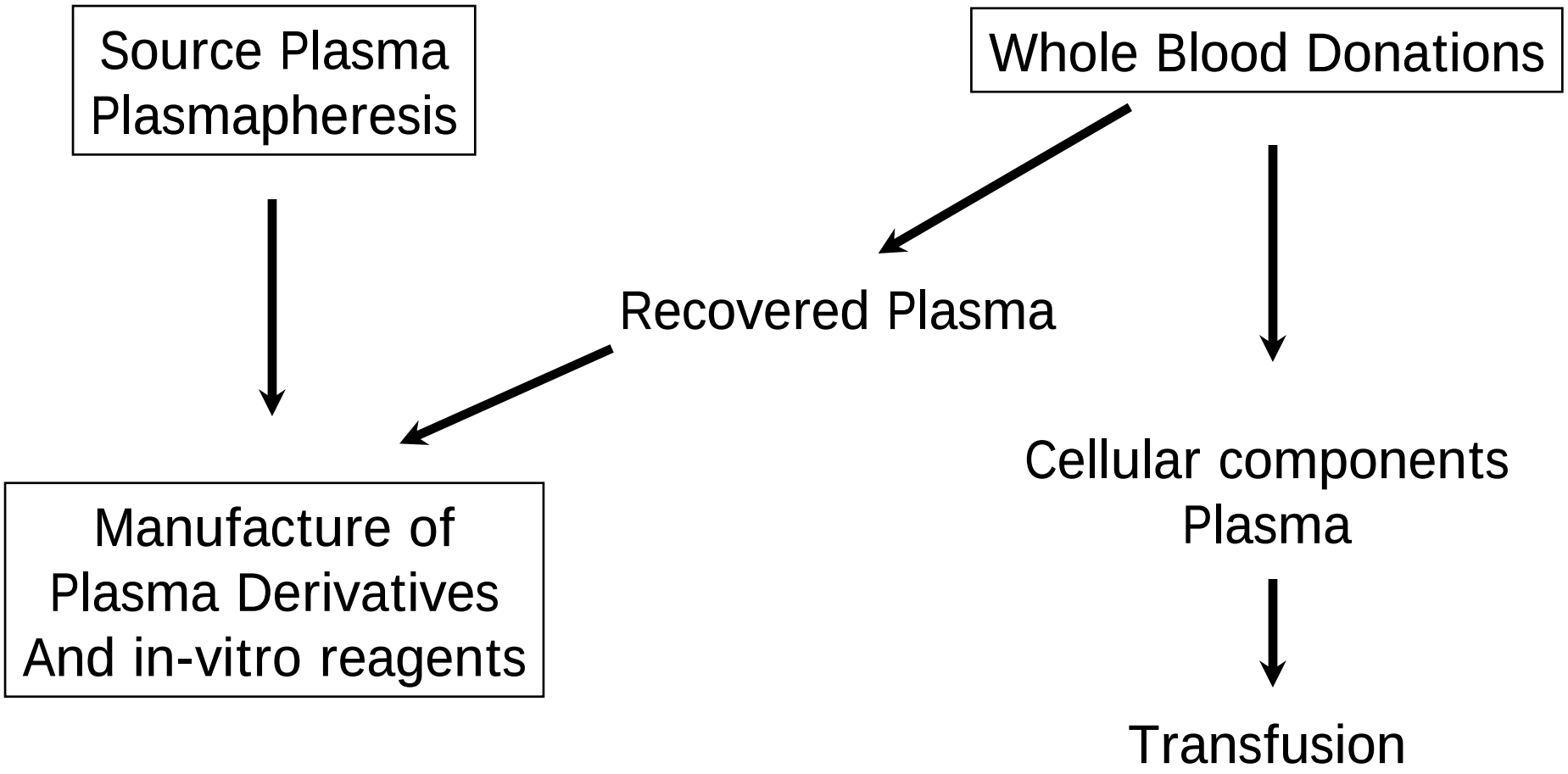
TOPICS TO BE COVERED

- Brief Introduction
  - Plasma Derivatives and Their Recombinant Analogues
- Critical Path
  - Facilitating New Technologies for Blood Product Safety and Efficacy
- Risk Management
  - Recent Advances in Blood Safety
- Harmonization
  - Cross-Center initiatives
  - Global Engagements

Source and Type of Regulated Blood Products



Yearly U.S. Blood Donation and Utilization

- 8 million unpaid volunteers donate approximately 14 million units of Whole Blood.
- About 23 million units of blood components are transfused into 4.5 million patients.
- Roughly 2.4 million units of “recovered plasma” from Whole Blood donation are sold for further manufacturing, including fractionation.
- 1 million paid apheresis donors provide an additional 10.5 million units of Source Plasma for fractionation.

Plasma-Derived Products and Their Recombinant Analogues

- Antihemophilic factor(AHF)
- AHF/von Willebrand factor complex
- Anti-inhibitor coagulant complex
- Coagulation factor IX
- Factor IX complex
- Fibrin sealant
- Thrombin

- Albumin
- Plasma protein fraction

- Alpha 1 proteinase inhibitor
- Anti-thrombin III

- Immune globulin: intravenous and intramuscular
- Cytomegalovirus immune globulin
- Hepatitis B immune globulin
- Rabies immune globulin
- Rho(D) immune globulin
- Tetanus immune globulin
- Vaccinia immune globulin
- Varicella-zoster immune globulin
- Botulism immune globulin

Recombinant AHFs, FVIIa, and FIX

Critical Path: Facilitating New Technologies for Product Development

- The concept of the Critical Path is to identify, focus upon and manage research efforts towards regulatory and scientific opportunities in order to improve the product development process and to promote the availability of needed products.
- **Examples:**
  - Novel Immune Globulins (IG) to Prevent or Treat Specific Diseases
  - Hemoglobin-Based Oxygen Carriers (HBOCs)
  - New Technologies for Detection of Blood Borne Pathogens
    - Facilitating bacterial detection devices to avoid transfusion of contaminated platelets
    - Developing microarray multiplex detection of blood-borne and BT pathogens

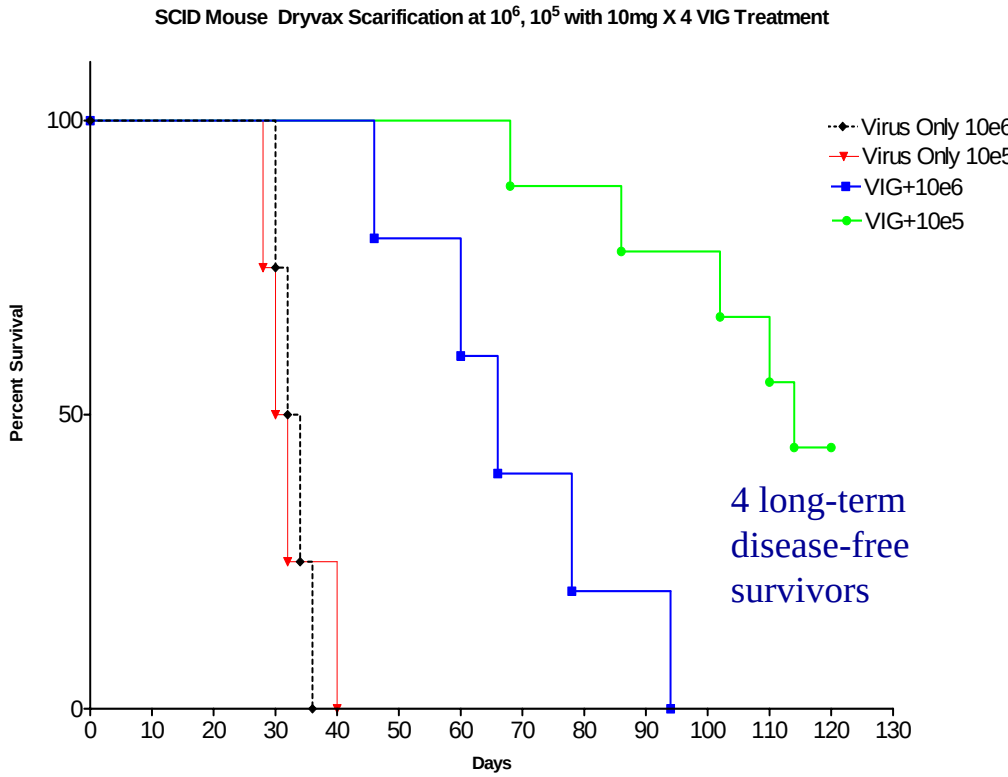
Immune Globulins as Counter Measures for Bioterrorism: Smallpox

- Public Health Issue:
  - Smallpox poses a bioterrorism threat likely to be addressed through mass vaccination. However, widespread vaccination is expected to cause fatalities in susceptible individuals.
  - Vaccinia immune globulins (VIG) are needed:
    - Progressive vaccinia
      - VIG reduces fatality: 100% → 50%
    - Eczema Vaccinatum
      - VIG reduces fatality: 30% → 3%
  - Studies of VIG cannot be done in humans

Immune Globulins as Counter Measures for Bioterrorism: Smallpox (Cont.)

- FDA Response:
  - Novel mouse model used to demonstrate that VIG can reduce vaccinia lethality in pre- and post-exposure treatment.
  - FDA's model was adopted by industry and used in support of licensure of the first VIGIV product
- Outcome:

  Many lives will be saved in any mass smallpox vaccination campaign

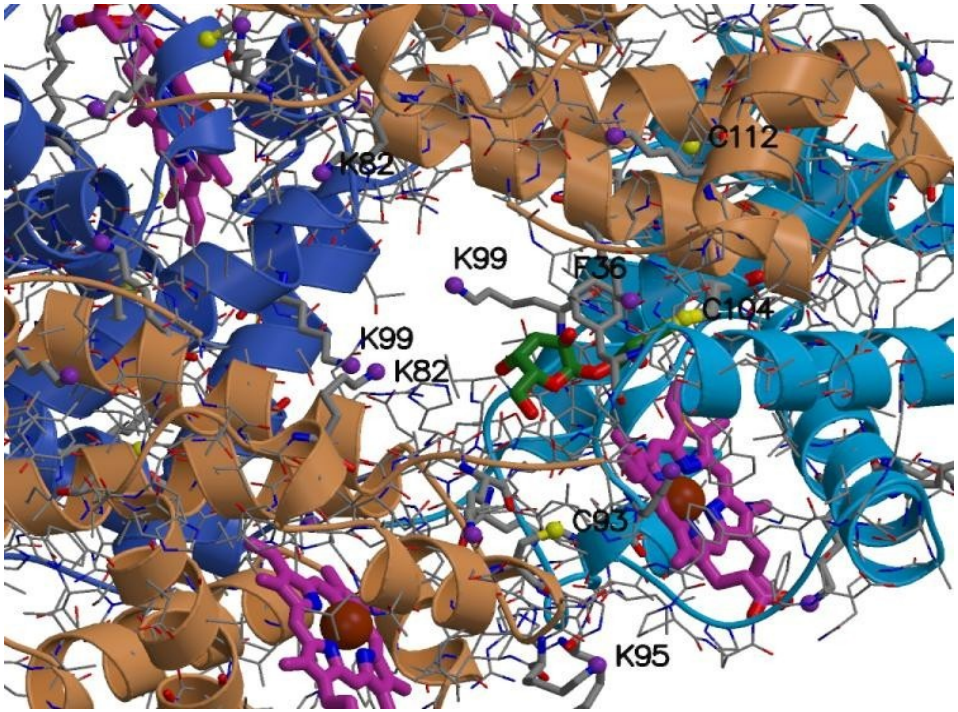


Hemoglobin-Based O_2 Carriers (HBOCs)

- Public Health Issue:

  Need for oxygen delivery to tissues in situations of bleeding where blood is not immediately available or acceptable
  - Trauma (battlefield, rural areas)
  - Religious reasons
  - Blood shortages
- FDA Response:
  - Characterization of HBOC structure-function
    - Effects of chemical modifications
  - Development of pre-clinical models to evaluate HBOC safety

Hemoglobin-Based O2 Carriers (Cont.)



FDA study showed cysteines modified instead of lysines

Outcomes:

- Established methods (e.g.mass spectroscopy) that distinguish between functional and non-functional HBOCs
- This technology enables improvement in product design and enhances potential for successful clinical trials

Boykins,Buehler, Alayash. Proteins (2005)

Recent Advances in Blood Safety
Addressing Emerging Threats: vCJD

- **Donor deferral policies since 1999**
- **TSEAC reviews twice yearly**
- **Studies reviewed on model TSE agent clearance in plasma derivatives**
- **Approval of analogous recombinant products made without animal proteins**
- **Cooperation with WHO in the development of TSE reference materials**
- **Research on prion detection and decontamination**

Recent Advances in Blood Safety; Addressing Emerging Threats: WNV

- **Issue:**
  - **Human to human WNV transmission by blood transfusion was first identified in 2002 thereby affecting the blood safety**
- **Actions:**
  - **In Nov. 2002 FDA provided criteria for approval of WNV NAT assay to test kit manufacturers**
  - **By July 2003 implementation of two investigational NAT assays occurred due to cooperative efforts among FDA and other DHHS agencies, public health labs, blood establishments and test kit manufacturers**
  - **FDA developed reference materials critical for implementation of sensitive NAT assays**
  - **FDA coordinate with CDC, NIH and blood banking establishments the epidemiological data on WNV infection and to monitor the out come of testing.**
  - **FDA recommended testing single donor samples instead of pooled samples at times and in areas experiencing a high rate of WNV infection.**
- **Outcome:**
  - **NAT screening interdicted > 1,600 infected donations, thereby preventing spread of WNV infection and possibly death through blood transfusion**
  - **FDA licensed one WNV NAT assay on Dec. 1, 2005 to screen blood, tissue, and organ donors thereby safeguarding the blood supply**

Harmonization

- Cross Center Initiatives
  - Cross Center Coordinating and Work Groups
    - CBER CMC CC
    - CDER OPS CC
      - Manufacturing science workgroup (WP)
    - WGs for guidances
  - Topics
    - Comparability
    - Follow-on protein products
    - PAT for biologics
    - “Design Space”
    - Others
- Global Engagements
  - ICH
    - Guidelines for Biotech/biological products
  - WHO
    - Expert Committee on Biological Standardization
    - Collaborating Center for Biological Standardization
  - International Society on Thrombosis and Hemostasis (ISTH), Scientific and Standardization Subcommittee (SSC)
  - WHO-ISTH liaison Group
  - Group of Experts for Blood Products (Observer)
    - USP and EP

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